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REMARKS

Applicants thank Examiner Helms for the courtesies extended during a personal interview with the undersigned on February 6, 2004 and in a further telephonic interview on March 30, 2004. The claims set forth above were discussed in the March 30 interview.

Prior to entry of the amendments set forth above, claims 1-5, 8-27 and 37-41 were pending. In the amendments presented above, claims 1-41 have been canceled and claims 42-63 have been added. Accordingly claims 42-63, including independent claims 42, 43, and 45, are thus pending for examination and reconsideration, which are respectfully requested in view of the foregoing amendments and following remarks.

In the August 1, 2003, office action, claims 1-5, 7-11, 13-17, 26-27, 37-38 and 41 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Johnson. Claims 1-5, 7, 10-11, 13-27 and 37-38 were rejected under 35 U.S.C. 103(a) as obvious over Johnson in view of Jenkins, Knappik, Dubel and Kostelny. Claims 1-5 and 13-27 were rejected under 35 USC § 112, second paragraph, as indefinite. Claim 27 was rejected under 35 USC § 101 as being directed to non-statutory subject matter. Claims 1-2, 4-5, 8-9, 12-13, and 26-27 were rejected under 35 USC § 102(e) as anticipated by Stevens. Claims 1-5, 8-27, 37-38 and 4 were rejected as obvious over Stevens in view of Jenkins, Knappik, Dubel and Kostelny. The specific grounds for rejection, and applicants response thereto, are set out in detail below.

Support for amendments

Intra-chain interface regions as recited in claims 42, 43, and 45 are described in the substitute specification filed August 29, 2003 at page 4, lines 1-7. Reducing the hydrophobicity of this region is described at page 4, lines 8-24. The remaining claims are supported throughout the specification and in the claims as originally filed.

Rejections under § 101

Claim 27 was rejected under 35 USC § 101 as being directed to non-statutory subject matter. Applicants respectfully submit that this rejection is mooted by the cancellation of claim 27. Applicants further submit that this rejection may not be applied to claim 62 which, like now-canceled claim 27, is directed to recombinant host cells. Specifically, the molecules encoded by the vectors contained in the claimed host cells are either single chain Fv (claim 42) or modified

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heavy or light chain variable domains (claims 43 and 45 respectively). Neither single chain Fv nor modified heavy or light chain variable domains occur in nature. Accordingly, host cells expressing such modified molecules also do not occur in nature and the rejection should not be applied to claim 62.

Rejections under § 102(b)

Claims 1-5, 7-11, 13-17, 26-27, 37-38 and 41 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Johnson. Specifically, the Examiner alleges that the modifications recited in the instant claims are taught by Johnson. To the extent that the same rejection is applied to the newly presented claims, applicants respectfully traverse.

In an antibody or antibody fragment the VH and VL domains are in separate polypeptide chains that interact to form a heterodimer that specifically binds antigen. It is well known that in such heterodimers the VH and VL domains interact via an interface between the distinct polypeptide chains *i.e.* an *inter-chain* interface. In such a heterodimer the hydrophobic residues in the inter-chain interface are shielded from exposure to solvent. In a single heavy chain (such as the "domain antibodies" described by Johnson) the hydrophobic residues at the inter-chain interface are exposed to solvent, which is energetically unfavorable.

In addition to the *inter-chain* VH/VL interface, the present inventors have recognized that each individual polypeptide chain in an intact antibody or antibody Fab fragment contains an *intra-chain* interface, *i.e.* an interface that occurs between domains within the same VH or VL chain. Thus, in an intact heavy chain (or in a Fab fragment), an intra-heavy chain interface occurs between regions of the VH and CH1 domains, and in the light chain, an intra-light chain interface occurs between the VL and CL domains. In intact antibody chains, or in Fab fragments, the hydrophobic residues in the intra-chain interface also are shielded from exposure to solvent.

Antibody fragments may be prepared that lack constant domains, for example, an Fv, a disulfide-linked Fv or a single chain Fv. The present inventors have recognized that, in such molecules, the hydrophobic residues in the variable domain intra-chain interface are exposed to solvent, with concomitant destabilization of the fragment. Surprisingly, replacement of amino acid residues in one or both of these interfaces to make the interface less hydrophobic significantly stabilizes the molecule.

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These modifications to the variable domain intrachain interface residues are quite distinct from the modifications described by Johnson, which are directed solely to modifications to the *interchain* interface residues that are intended to stabilize so-called "domain antibodies" (single heavy domain molecules). Moreover, Johnson's domain antibodies, by definition, are not intended to interact with a second variable domain to form a functional antigen binding molecule, but rather are intended to bind antigen without a second variable domain.

It is axiomatic that, for a prior art reference to be anticipatory, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990). Johnson does not teach modifying an amino acid residue in an intrachain interface and, accordingly, does not teach each and every element of the invention and the rejection should be withdrawn.

Rejections under § 102(e)

Claims 1-2, 4-5, 8-9, 12-13, and 26-27 are rejected under 35 USC § 102(e) as anticipated by Stevens. Specifically, the Examiner alleges that Stevens teaches modifications of the inter-domain interface that increase the hydrophilicity of an antibody or antibody fragment. Applicants respectfully traverse.

Stevens teaches a single substitution at position 38 (corresponding to position 46 in the numbering scheme of the instant application) in single variable light chains, with the intention of promoting formation of light chain-light chain dimmers. See column 9 generally. This position is not in an intrachain interface region. Accordingly, Stevens fails to teach each and every limitation of the claimed invention and the rejection should be withdrawn.

Rejections under § 103(a)

Claims 1-5, 7, 10-11, 13-27 and 37-38 are rejected under 35 U.S.C. 103(a) as obvious over Johnson in view of Jenkins, Knappik, Dubel and Kostelny. Claims 1-5, 8-27, 37-38 and 4 are rejected as obvious over Stevens in view of Jenkins, Knappik, Dubel and Kostelny. Applicants respectfully traverse.

For the reasons described above, Johnson fails to teach or suggest modification of residues in the intrachain interface region. Instead, Johnson suggests the modification of amino

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acids at the interchain interface of a "single variable domain" that otherwise would interact with its variable domain complement. Similarly, Stevens allegedly describes a method of modifying a light chain to promote self-dimerization and fails to the modifications recited in the instant claims. None of the secondary references make up for the deficiencies of Johnson or Stevens, or would have suggested to one of ordinary skill in the art that modifying the teachings of Johnson or Stevens would somehow lead to the claimed invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 103(a).

Rejections under § 112, second paragraph

Claims 1-5 and 13-27 are rejected under 35 USC § 112, second paragraph, as indefinite. Specifically, the Examiner alleges that various terms in the claims are undefined and/or unclear. Applicants respectfully submit that these rejections are moot in light of the claim amendments presented herein.

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Conclusion:

In view of the foregoing, applicants respectfully submit that the case is in condition for allowance. The Examiner is invited to contact the undersigned attorney to resolve any issues, in order to expedite the prosecution of the application.

Respectfully submitted,

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Date

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